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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	09/707,737
Filing Date	November 6, 2000
First Named Inventor	Stephen Quake
Group Art Unit	1655
Examiner Name	Arun K. Chakrabarti
Total Number of Pages in This Submission: 1	Attorney Docket Number: 20174C-001810US

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ENCLOSURES *(check all that apply)*

☒ Fee Transmittal Form	☐ Assignment Papers *(for an Application)*	☐ After Allowance Communication to Group
☐ Fee Attached	☐ Drawing(s)	☐ Appeal Communication to Board of Appeals and Interferences
☒ Amendment / Response	☐ Licensing-related Papers	☐ Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
☐ After Final	☐ Petition Routing Slip (PTO/SB/69) and Accompanying Petition	☐ Proprietary Information
☐ Affidavits/declaration(s)	☐ Petition to Convert to a Provisional Application	☐ Status Letter
☒ Extension of Time Request	☐ Power of Attorney, Revocation Change of Correspondence Address	☒ Other Enclosure(s) *(please identify below)*: Return Postcard
☐ Express Abandonment Request	☐ Terminal Disclaimer	
☐ Information Disclosure Statement	☐ Request for Refund	
☐ Certified Copy of Priority Document(s)	☐ CD, Number of CD(s)	
☐ Response to Missing Parts/ Incomplete Application	Remarks: The Commissioner is authorized to charge any additional fees to Deposit Account 20-1430.	
☐ Response to Missing Parts under 37 CFR 1.52 or 1.53		

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm and Individual name	Townsend and Townsend and Crew LLP Hugh Wang Reg. No. 47,163
Signature	
Date	May 24, 2002

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on this date: May 24, 2002

Typed or printed name	Kathy Johnston		
Signature		Date	May 24, 2002

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FEE TRANSMITTAL for FY 2001

Patent fees are subject to annual revision.

Complete if Known	
Application Number	09/707,737
Filing Date	November 6, 2000
First Named Inventor	Stephen Quake
Examiner Name	Arun K. Chakrabarti
Group Art Unit	1655
Attorney Docket No.	20174C-001810US

TOTAL AMOUNT OF PAYMENT ($) 460

METHOD OF PAYMENT

1. ☒ The Commissioner is hereby authorized to charge indicated fees and credit any over payments to:

Deposit Account Number: 20-1430

Deposit Account Name: Townsend and Townsend and Crew LLP

☒ Charge Any Additional Fee Required Under 37 CFR 1.16 and 1.17

☒ Applicant claims small entity status. See 37 CFR 1.27

2. ☐ **Payment Enclosed:**

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FEE CALCULATION

1. BASIC FILING FEE

Large Fee Code	Large Entity Fee ($)	Small Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	740	201	370	Utility filing fee	
106	330	206	165	Design filing fee	
107	510	207	255	Plant filing fee	
108	740	208	370	Reissue filing fee	
114	160	214	80	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES

			Extra Claims		Fee from below		Fee Paid
Total Claims		-20**		X		=	
Independent Claims		-3**		X		=	
Multiple Dependent				X		=	

Large Fee Code	Large Entity Fee ($)	Small Fee Code	Small Entity Fee ($)	Fee Description
103	18	203	9	Claims in excess of 20
102	84	202	42	Independent claims in excess of 3
104	280	204	140	Multiple dependent claim, if not paid
109	84	209	42	** Reissue independent claims over original patent
110	18	210	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Fee Code	Large Entity Fee ($)	Small Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet.	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	400	216	200	Extension for reply within second month	
117	920	217	460	Extension for reply within third month	460
118	1,440	218	720	Extension for reply within fourth month	
128	1,960	228	980	Extension for reply within fifth month	
119	320	219	160	Notice of Appeal	
120	320	220	160	Filing a brief in support of an appeal	
121	280	221	140	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive – unavoidable	
141	1,280	241	640	Petition to revive – unintentional	
142	1,280	242	640	Utility issue fee (or reissue)	
143	460	243	230	Design issue fee	
144	620	244	310	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	180	126	180	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	740	246	370	Filing a submission after final rejection (37 CFR § 1.129(a))	
149	740	249	370	For each additional invention to be examined (37 CFR § 1.129(b))	
179	740	279	370	Request for Continued Examination (RCE)	
169	900	169	900	Request for expedited examination of a design application	
Other fee (specify)					

The Commissioner is authorized to charge any additional fees to the above noted Deposit Account.

*Reduced by Basic Filing Fee Paid SUBTOTAL (3) ($)460

SUBMITTED BY				Complete (if applicable)	
Name (Print/Type)	Hugh Wang	Registration No. (Attorney/Agent)	47,163	Telephone	650-326-2400
Signature				Date	May 24, 2002

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PATENT
20174C-001810US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Stephen Quake et al.

Application No.: 09/707,737

Filed: November 6, 2000

For: Methods And Apparatus For Analyzing Polynucleotide Sequences

Examiner: Arun K. Chakrabarti

Art Unit: 1655

Response To Office Action

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This is in response to the Office Action mailed December 5, 2001 in the above-identified application. Reconsideration is respectfully requested in view of the following amendments and remarks. A petition for extension of time and the appropriate fees accompany this Response.

AMENDMENTS

In the Title:

Please amend the title to read as follows. A clean version of the amendment is shown in the Appendix.

-- Methods And Apparatus[**es**] For Analyzing Polynucleotide Sequences --

In The Claims:

Please amend the claims as follows. A clean version of all pending claims is shown in the attached Appendix.

1. (Amended) A method of analyzing a target polynucleotide comprising:

(a) providing a primed target polynucleotide attached to a microfabricated multilayer elastomeric synthesis channel;

(b) flowing a first nucleotide through the synthesis channel under conditions whereby the first nucleotide attaches to the primer, if a complementary nucleotide is present to serve as template in the target polynucleotide;

(c) determining presence or absence of a signal, the presence of a signal indicating that the first nucleotide was incorporated into the primer, and hence the identity of the complementary base that served as a template in the target polynucleotide;

(d) removing or reducing the signal, if present; [**and**]

(e) repeating steps (b)-(d) with a further nucleotide, the same or different from the first nucleotide, whereby the further nucleotide attaches to the primer or a nucleotide previously incorporated into the primer, and

(f) repeating step (e) until identities of the bases in a portion or all of the target polynucleotide are determined.

2. (Amended) The method of claim 8, wherein said microfluidic chip is fabricated with an elastomeric [**materia**] material.

3. (Amended) A method of analyzing a target polynucleotide comprising::.

(a) pretreating the surface of a substrate with a polyelectrolyte multilayer (PEM) to create surface chemistry that facilitates polynucleotide attachment and sequence analysis;

(b) providing a primed target polynucleotide attached to a surface of a substrate;

(c) providing a labeled first nucleotides to the attached target polynucleotide under conditions whereby the labeled first nucleotide attaches to the primer, if a complementary nucleotide is present to serve as template in the target polynucleotide;

(d) determining presence or absence of a signal, the presence of a signal indicating that the labeled first nucleotide was incorporated into the primer, and hence the identity of the complementary base that served as a template in the target polynucleotide; [**and**]

(e) repeating steps (c)-(d) with a labeled further nucleotide, the same or different from the first labeled nucleotide, whereby the labeled further nucleotide attaches to the primer or a nucleotide previously incorporated into the primer, and

(f) repeating step (e) until identities of the bases in a portion or all of the target polynucleotide are determined..

4. (Amended) A method of analyzing a target polynucleotide comprising:

(a) providing a primed target polynucleotide in a microfabricated multilayer elastomeric synthesis channel;

(b) providing a first nucleotide under conditions whereby the first nucleotide attaches to the primer, if a complementary nucleotide is present to serve as template in the target polynucleotide; wherein a [**fraction**] percentage of molecules of said first nucleotide is labeled.

(c) determining presence or absence of a signal from the primer, the presence of a signal indicating the first nucleotide was incorporated into the primer, and hence the identity of the complementary base that served as a template in the target polynucleotide; [**and**]

(d) repeating steps (b)-(c) with a further nucleotide, the same or different from the first nucleotide, whereby the further nucleotide attaches to the primer or a nucleotide previously incorporated into the primer; wherein a [**fraction**] percentage of molecules of said further nucleotide is labeled, and

(e) repeating step (d) until identities of the bases in a portion or all of the target polynucleotide are determined..

5. (Amended) The method of claim 36, wherein said [**fraction**] percentage of the first nucleotide and said [**fraction**] percentage of the further nucleotide are less than 10%.

6. (Amended) The method of claim 37, wherein said [**fraction**] percentage of the first nucleotide and said [**fraction**] percentage of the further nucleotide are less than 1%.

7. (Amended) The method of claim 38, wherein said [**fraction**] percentage of the first nucleotide and said [**fraction**] percentage of the further nucleotide are less than 0.1%.

8. (Amended) The method of claim 34, wherein said [**fraction**] percentage of the first nucleotide and said [**fraction**] percentage of the further nucleotide are less than 0.01%.

Status of the Application and the Present Amendment

Claims 1 to 40 are pending and stand rejected in the application. With entry of the present amendment, claims 1, 11, 26, 34, and 37-40 have been amended. Support for the recitation of "multilayer elastomeric synthesis channel" in claims 1 and 34 is replete in the specification, e.g., at page 17, lines 27-30. The recitation of "polyelectrolyte multilayer (PEM)" in amended claim 26 has support in the specification, e.g., at page 4, line 17. Support for the recitation of percentage of labeled nucleotides in amended claims 34 and 37-40 is provided in the specification, e.g., at page 34, lines 1-7.

Applicants note that the claim amendments are made to correct typographical error, to improve clarity, or to expedite prosecution, and should not be viewed as acquiescence of any ground of rejection unless otherwise noted. No new matter has been added by the present amendment.

The following remarks address issues raised in the Office Action.

Rejection Under 35 U.S.C. 112, 2nd Paragraph

The Office Action makes various rejections of the pending claims based on alleged indefiniteness. Each of the rejections is addressed below. As an initial matter, Applicants note that an indefiniteness rejection should not be based on reading the claim language in abstract. Rather, as stated in the MPEP:

> Definiteness of claim language must be analyzed, not in a vacuum, but in light of:
> (A) The content of the particular application disclosure;
> (B) The teachings of the prior art; and
> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.
> [MPEP § 2173.02 at 2100-194]

Claims 1, 26, and 34 are rejected as allegedly lacking a step which relates back to the preamble. Although Applicants respectfully traverse this rejection, to facilitate prosecution of the subject application, the claims have been amended by adding an additional step which clearly relates back to the preamble in the preamble.

Claim 11 was rejected for the recitation of "elastomeric material." The Office Action states that it is not clear if elastomeric materials are claimed or a novel and special type of fabrication is claimed. Applicants respectfully traverse the rejection. First, claim 11 is a dependent claim which depends from claims 8, 4, and 1. Patentability of claim 11 does not reside on "elastomeric material" or fabrication method recited in the claim. Rather, these elements further limit the scope of the claims from which claim 11 depends. The elastomeric materials and fabrication methods of claim 11 do not have to be novel in order to be patentable.

In addition, there is no indefiniteness in the meaning or boundary of "elastomeric materials" or "fabrication." "Fabrication" has its ordinary meaning, i.e., to manufacture or to produce. Elastomeric material is a routinely used term that is well known in the art. As defined in *The American Heritage Dictionary* (2nd College Ed., Houghton Mifflin Co., Boston, 1991), "elastomer" refers to "any of various polymers having the elastic properties of natural rubber." The specification also provides extensive discussion of elastomeric materials that are suitable for the present invention. For example, the specification discloses the physicochemical properties of elastomers (at page 17, lines 10-22) and a number of suitable elastomeric materials for the invention (page 17, lines 24-27). As such, Applicants submit that there is no indefiniteness in claim 11.

Claims 37-40 are rejected as allegedly indefinite in the recital of "fraction of" the nucleotide. While Applicants respectfully disagree with the assertion, Applicants have amended claims 34 and 37-40 to replace "fraction" with "percentage of molecules" to make it clearer that some copies of the nucleotide molecules, not parts of each molecule, are labeled.

In light of the above claim amendments and remarks, Applicants submit that there is no indefiniteness in the presently pending claims. The instant rejections should therefore be withdrawn.

Rejection Under 35 U.S.C. 102

Claims 1-7, 13, 15-21, 26-28, and 34-36 are rejected under 35 U.S.C. 102(e) as allegedly anticipated by Livak et al. (U.S. Patent No. 5,945,284). The Office Action alleges that each element of the rejected claims is taught in Livak et al.

Although Applicants respectfully traverse the rejections of claims 1-7, 13, 15-21, and 34-36, in an effort to further expedite prosecution, claims 1 and 33 has been amended to specify that

the synthesis channel is microfabricated with multilayer elastomer. Livak et al. do not teach multilayer elastomeric microfluidic device. For at least this reason, claims 1 and 33, as well as dependent claims 2-7, 13, 15-21, and 34-36 are novel over Livak et al.

Turning to the rejection of claims 26-28, the Office Action states that Livak et al. teach pretreating the surface of substrate to create surface chemistry that facilitates polynucleotide attachment and sequence analysis. Applicants respectfully disagree. The section of Livak et al. that was cited in the Office Action, Col. 7, line 35 to Col. 8, line 42, does not contain such teachings. Rather, it discussed different materials that can be used as solid phase support, and their possible sizes, shapes, and other characteristics. Livak et al. at most suggested that the solid substrate can include different linking molecules. However, there is no discussion of pretreating the surface of a solid support to create favorable surface chemistry for immobilizing polynucleotides.

Also, contrary to the assertion in the Office Action, there is no discussion in Livak et al. of coating a solid support with a polyelectrolyte multilayer terminated with a polyanion. The section cited in the Office Action, Col. 8, lines 19-42, only discusses immobilizing primer/template with, e.g., a biotin-avidin linkage. By contrast, in the present invention, creation of surface chemistry on synthesis channels are prior to and a separate step from immobilization of the primer or templates (see, e.g., page 29, lines 7-16). Thus, claims 26-28 are novel over Livak et al. at least on these grounds.

In light of the above amendments and clarifications, Applicants respectfully request that the instant rejection be withdrawn.

Rejection of Under 35 U.S.C. 103

Citing Livak et al. and a number of other references, the Office Action also makes a few rejections of the present claims as allegedly obvious. Applicants respectfully traverse these rejection. Before addressing each of the rejections, Applicants will provide a brief summary of the subject invention and its advantages over the prior art.

The present invention is predicated in part on the employment of microfluidic devices fabricated from multilayer elastomer structures. As disclosed extensively in the specification, multilayer structures are constructed by bonding layers of elastomer, each of which is separately cast, e.g., from a micromachined mold. The elastomer is a two-component addition-cure silicone

rubber. Because each layer has an excess of one of the two components, reactive molecules remain at the interface between the layers. Further curing causes the two layers to irreversibly bond. The device thus created is a monolithic three-dimensionally patterned structure composed of entirely of elastomer.

As reported in Unger et al., *Science* 288:113-116, 2000 (referenced in the specification, at page 13, line 28; also cited as Reference "BQ" in the Information Disclosure Statement submitted on March 5, 2001), multilayer elastomeric microfluidic devices represent a significant advance in the art (e.g., as compared to the traditional micro-machining methods). Numerous advantages are provided by the microfabricated fluidic devices in accordance with the present invention. For example, the monolithic elastomeric microfluidic devices can be actuated with surprising speed, permits exceptionally low dead volumes (see also the specification, at page 13, lines 2-4). In addition, because different layers (or parts) of the device are usually composed of the same elastomer, interlayer adhesion failures and thermal stress problems are completely avoided. Interlayer adhesion and thermal stress buildup are problems endemic to conventional micromachining. Also, the elastomer is a soft material allowing large deflections with small actuation forces. Further, the monolithic elastomeric microfluidic devices avoid several practical problems affecting flow systems based on electroosmotic flow or dielectrophoresis, such as electrolytic bubble formation around the electrodes and a strong dependence of flow on the composition of the flow medium. Electrolytic bubble formation seriously restricts the use of electroosmotic flow in integrated microfluidic devices.

With the above-discussed features and advantages of the present invention in mind, the following remarks address each of the rejections made under 35 U.S.C. 103.

Claims 1-7, 13, 15-21, 26-28, and 34-40 are rejected over Livak et al. The Office Action states that while Livak et al. do not teach less than 0.01% of labeled nucleotides, such would have been obvious. In response, Applicants note that Livak et al. do not teach or suggest, expressly or implicitly, microfabricated multilayer elastomeric synthesis channels for immobilizing polynucleotides. Livak et al. only alluded to the possibility of using micromachined chips as solid phase support (Col. 7, line 41). However, as discussed above, micromachined chips are quite different from the microfabricated elastomeric devices of the present invention. The disadvantage of traditional micromachining are discussed in more detail in Unger et al., supra, and parent

Application Serial No. 09/605,520. In addition, as noted earlier, Livak et al. also do not suggest coating the surface of the solid support to create surface chemistry that facilitates nucleotide attachment. Therefore, claims 1-7, 13, 15-21, 26-28, and 34-40 are nonobvious over Livak et al.

Claims 1-11, 13-21, 26-28, and 34-40 are also rejected as allegedly obvious over Livak et al. in view of Effenhauser et al. (Analy. Chem. 69:3451-3457). The Office Action states that Effenhauser et al. teach bonding a microfluidic chip fabricated with an elastomer to a flat substrate. Applicants traverse this rejection. First, there would have been no motivation to combine the teachings of Livak et al. with Effenhauser et al. As discussed above, Livak et al. at most suggested using micromachined chips. On the other hand, Effenhauser et al. relates to a different method of microfabrication, soft lithography (see, Unger et al. in which Effenhauser et al. is cited as reference 16). In addition, even assuming for the sake of discussion that one would be motivated to combine the teachings of these two references, one would not be led to the presently claimed invention. This is because Effenhauser et al. at most showed fabrication of one elastomer layer. Multilayer elastomer microfluidic devices were only taught and enabled by the present inventors, e.g., as demonstrated in Unger et al. Thus, the present claimed invention is also nonobvious over Livak et al. in view of Effenhauser et al.

Claims 1-21, 26-28, and 34-40 are also rejected as allegedly obvious over Livak et al. in view of Effenhauser et al. and further in view of Koster et al. (US Patent 6,225,567). The Office Action states that Koster et al. teach the elastomeric material RTV silicone. In response, Applicants note that Koster et al. do not make up for the lack of teaching of a multilayer elastomeric microfluidic device in Livak et al. and Effenhauser et al. Therefore, the present invention is nonobvious over the cited references.

The Office Action further makes rejections of the present invention as allegedly obvious, citing a few more references in addition to the above-discussed art. However, Applicants note that none of these references, Williams et al. (US Patent 6,232,075), Clark et al. (US Patent 6,242,528), Batz et al. (US Patent 6,225,052), and Liu et al. (US Patent 6,165,694), teach or suggest use of multilayer elastomeric synthesis channel in analyzing polynucleotide sequence. Thus, even assuming that one would be motivated to combine teachings of the cited art, which is denied, the present invention is nonetheless nonobvious because the combined teachings of the cited references do not teach or suggest each element of the presently claimed invention.

In light of the above explanations and clarifications, Applicants submit that the presently claimed invention is non-obvious over the cited references and respectfully request withdrawal of all the rejections under 35 U.S.C. 103.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

Hugh Wang
Reg. No. 47,163

Appendix Clean version of amendments

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